SECTION II
REMARKS

Regarding the Amendments

Claims 1, 2, 5, and 11 have been amended as set forth in the above Complete Listing of the Claims. As amended, the claims are supported by the specification and the original claims. No new matter has been added, as defined by 35 U.S.C. § 132.

Thus, upon entry of the amendments, claims 1-21 will be pending, of which claims 12-21 are withdrawn.

Priority Claim

The examiner's granting of the benefit of priority to the filing date of U.S. Patent Application No. 09/058113, filed April 9, 1998, is acknowledged.

Claim Rejections Under 35 U.S.C. § 112, 1st paragraph, enablement

The examiner has withdrawn the prior rejection of claims 1-11 under 35 U.S.C. §112, first paragraph, as lacking enablement and has provided a new enablement rejection. In the Office Action mailed July 11, 2007, claims 1-11 are rejected for a CD4 transgenic rat where the rat is adapted to model HIV infection (pages 6-7), for a transgenic rat that mediates entry of HIV-1 into PBMC (pages 7-8), for a CD4/CXCR4 or CD4/CCR5 transgenic rat that models human HIV infection (pages 8-10), for a transgenic rat that binds gp120 and does not mediate HIV infection as a model for human HIV infection (page 10), and for mediation of entry of any other HIV virus other than HIV-1 into PBMC of the transgenic rat (pages 10-11). Applicants respectfully disagree.

Regarding use of a CD4-only transgenic rat, the examiner has pointed to the language at page 4, paragraph 2 of the specification as demonstrating that CD4 alone cannot model human HIV infection. The examiner's attention is respectfully drawn to the amended language of claim 1, where it is claimed that the CD4 "transgenic rat is a model of human HIV binding." As such a transgenic rat as a model of HIV binding to gp120 is enabled by the present invention.

Additionally, the examiner has rejected claims 1, 3, and 11 as nonenabled for a transgenic rat (CD4, CD4/CCR5, or CD4/CXCR4) that is adapted to model human HIV infection or that is

capable of mediating entry of HIV. It is the examiner's assertion that these claims are not enabled, as generation of transgenic mice are not predictive of generation of transgenic rats. Applicants agree that alone, transgenic mice are not predictive of transgenic rats, but taken in combination with the teachings in the art of transgenic rats and in combination with the teachings of the specification, particularly at pages 22-24 and in Example 12, page 51, one of skill in the art would be enabled to generate CD4, CD4/CCR5, or CD4/CXCR4 transgenic rats that are models of human HIV binding (amended claim 1), model human HIV infection or are capable of mediating entry of HIV. In particular, the specification provides detailed directions and specific characteristics of a transgenic animal according to the invention. In particular such an animal may be transgenic in all cells, or may be a mosaic animal, the animal must express the desired proteins, and the application provides methods of quantification of viral load in the animals. Additionally, the examples provide for uses of the animals in *in vitro* (p. 25-26) and *in vivo* (p. 26-28) assays in order to identify lentiviral therapeutics. Accordingly, one of skill in the art would have combined the teachings in the art with the teachings of the application to make and/or use the invention. Accordingly, the claims are enabled under 35 U.S.C. §112, first paragraph.

The examiner also states that "the art suggest[s] that [there] are additional factors unique to human HIV-1 infection that are not being accounted for in the art recognized transgenic mice" and therefore "the art suggests that more factors need to be present in transgenic animal models than CCD4 and CCR5 or CXCR4 to model human HIV infection..." By such statement the examiner is again making a leap between transgenic mice models and transgenic rat models. In fact, the statements made by the examiner show that mouse HIV models may need more factors to model human HIV infection, however, mouse models are not directly relevant to rat models.

As applicants have previously asserted in detail, mice and rats are not directly predictive of one another as transgenic models, as the genomes of these animals are considerably different. Furthermore, applicants have acknowledged that transgenic mice previously generated in the art have not closely modeled human infection of HIV (specification, page 5). Accordingly, one of skill in the art would not have expected a transgenic mouse to model human HIV infection. The examiner's statement with respect to the teachings of Browning et al. state that "[t]aken together these results suggest that although expression of human CD4 and a chemokine receptor such as CCR5 may be sufficient to permit entry of HIV-1 into mouse cells...the presence of additional

blocks that prevent efficient HIV replication in mouse cells complicates the use of transgenic mice to investigate the immunopathology of HIV-1 infection."

In fact, applicants have directly addressed this failure of mice models to transmit HIV between cells, on page 5 of the present application. Such failure is attributable to the lack of expression of gp120 on the surface of murine T-cells, preventing transmission of HIV from one cell to another in mice. In rats, however, as can be seen in the Figures of the present application, rat PBMCs do express gp120 on their surface. Thus, one of skill in the art would reasonably assume that a rat model is superior to a mouse model in modeling human HIV infection and would have no basis for assuming that the claimed transgenic rats "require additional factors to model human HIV infection," as alleged by the examiner. Accordingly, based on the failings shown in previous mice models, and the teachings of the invention, one of skill in the art would be enabled to make a transgenic rat model for human HIV infection without a need for cofactors additional to CD4, CCR5 and CXCR4.

Additionally, the examiner alleges that the teachings of the prior art show that certain regions of CD4 and gp120 are necessary for the two to bind and mediate entry of an HIV virus and that the claims "encompass portions of the CD4 that would not [sic] encompass the regions that bind but do not mediate HIV infection." (Office Action mailed July 11, 2007, page. 10.) In support of such assertion, the examiner cites the Farrar et al. (Crit. Rev. Immunol., 8(4):315, abstract, 1988) and Reeves and Doms (J. Gen. Virol., 83: 1253-1265, 200) references, as teaching that "certain regions and interaction sites on the CD4 and gp120 are necessary for CD4 to bind to gp 120 and mediate HIV infection." (Office Action mailed July 11, 2007, page 10.) Applicants agree with the examiner's statements that specific portions of the CD4 are required to bind gp120. Accordingly the claims of the present application are so limited, in reciting "at least a portion of a CD4 protein sufficient for binding to gp120..." (emphasis added). Nothing in the references cited by the examiner, however, states that additional sections of CD4 beyond those required for binding gp120 are required to mediate a subsequent conformational change to gp120, rendering it receptive to coreceptor binding and mediation of HIV infection. Accordingly, as long as the claimed portion of CD4 is capable of binding gp120, such subsequent conformation of gp120 to allow cofactor binding and mediation of HIV infection may occur.

Amended claim 1, recites a model of human HIV binding. Accordingly, the model of that claim does not require mediation of HIV infection. Claims 2-10 and independent claim 11, recite models of human HIV infection, including the presence of coreceptors CCR5 and CXCR4, both

shown to mediate HIV entry after binding of gp120. Accordingly, one of skill in the art would be enabled to make a transgenic rat including at least a portion of a CD4 protein sufficient for binding to gp120 and using such transgenic rat as a human model, as claimed.

Last, the examiner rejects the claims as non enabled with respect to HIV strains other than HIV-1. As the amended claims recite models of HIV-1 binding and infection, it is respectfully submitted that this portion of the rejection is moot. Withdrawal of the rejection is respectfully requested.

As set forth in detail above, all aspects of pending claims 1-11 rejected under 35 U.S.C. §112, first paragraph, as lacking enablement are enabled. Accordingly, withdrawal of the rejection of these claims is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, 1st paragraph, written description

The Examiner has rejected claims 1-11 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement with respect to a transgenic rat comprising a transgene encoding a portion of a CD4 protein and a portion of CCR5.

Initially, it is noted that claim 11 should not be included within this rejection, as that claim does not recite a transgenic rat comprising a transgene encoding a portion of a CD4 protein and a portion of CCR5.

The examiner's attention is respectfully drawn to amended claims 2 and 5, which no longer contain language reciting a portion of CCR5. These claims have been amended in accordance with the recitation of the CXCR4 coreceptor in claim 11, where the transgene encodes the full-length protein.

As such, the rejection is moot and withdrawal of the rejection of claims 1-11 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, 1st paragraph, new matter

The withdrawal of the rejection of claim 5 under 35 U.S.C. §112, first paragraph as containing new matter is acknowledged.

In the Office Action mailed July 11, 2007, the examiner has rejected claims 1-11 under 35 U.S.C. §112, first paragraph, as containing subject matter which would be considered new matter with regard to the recitation of the language "wherein the transgenic rat is adapted to model human HIV infection" in claims 1 and 11 of the application.

Initially the examiner's attention is respectfully drawn to the amendments section set forth above. Both claims 1 and 11 have been amended such that they no longer require that the transgenic rat be adapted to model human HIV binding or infection, but that the rat is a model of human HIV binding or infection. As such, the transgenic rat models the infection and disease progression of HIV as it occurs in humans. Such modeling is supported in the specification at page 5, lines 19-23, where non-human transgenic models of disease progression are discussed; page 6, lines 8-16 regarding the expression of transgenes related to HIV infection; page 6, lines 17-21 regarding exhibition of a symptom or phenotypic characteristic of human HIV infection and or development of AIDS (disease progression); the Figures and Examples show characteristics of HIV-transgenic rats, comparable to HIV infection and disease progression in humans; Example 9, in particular, directly compares the pathology of an HIV transgenic rat with that of HIV human subjects. The specification clearly shows that a transgenic rat, infected with HIV-1 will model the infections patterns and disease progression as seen in humans. Accordingly, the application clearly describes use of a transgenic rat as a model for human HIV binding or infection. Recitation of such language in the claims is supported by the specification and does not constitute new matter, as defined by 35 U.S.C. §112, first paragraph. Withdrawal of the rejection is therefore respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, 2nd paragraph, definiteness

The withdrawal of the rejection of claim 5, under 35 U.S.C. §112, second paragraph, as being indefinite in its recitation of the language "the transgene," is acknowledged.

In the Office Action mailed July 11, 2007, the examiner has rejected claims 1 and 11 under 35 U.S.C. §112, second paragraph as indefinite for recitation of the language "wherein the transgenic rat is adapted to model HIV infection." Specifically, the examiner objects to use of the term "adapted" in the claim. The examiner's attention is respectfully drawn to amended claims 1 and 11, which no longer contain the term "adapted." As such, withdrawal of the

rejection of claims 1 and 11 under 35 U.S.C. §112, second paragraph as indefinite is respectfully requested.

Additionally the examiner has rejected claim 5 under 35 U.S.C. §112, second paragraph as indefinite for recitation of the language "capable of mediating entry of HIV." Specifically, the examiner objects to this language, as not specifying what the HIV is entering into. The examiner's attention is respectfully drawn to amended claim 5, as set forth above, which recites "capable of mediating entry of HIV into the PBMC on which the at least a portion of CD4 is expressed." As such, it is clear that the HIV enters the cell and withdrawal of the rejection of claim 5 under 35 U.S.C. §112, second paragraph as indefinite is respectfully requested.

Claim Rejections Under 35 U.S.C. §102

The rejection of claims 1-11, under 35 U.S.C. §102(e) as being anticipated by Goldsmith et al (U.S. Pat No. 6,372,956 B1 4/16/2002; filing date 12/23/1999), is withdrawn. No additional rejections under 35 U.S.C. §102 are provided.

THE REMAINDER OF THIS PAGE IS INTENTIONALLY LEFT BLANK

4115-150-CIP-DIV

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-11 are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the July 11, 2007 Office Action without extension was set at three months, or October 11, 2007. This response is therefore timely and no fees are believed to be due for the filing of this paper. However, should any fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

Date: October 11, 2007

Steven J. Hultquist
Reg. No. 28,021
Attorney for Applicants

Date: October 11, 2007

Kelly K. Reynolds
Reg. No. 51,154
Attorney for Applicants

**INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File No.: 4115-150-CIP-DIV-RCE**

The USPTO is hereby authorized to charge any deficiency or credit any overpayment of fees properly payable for this document to Deposit Account No. 08-3284